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Effect of sevoflurane anaesthesia on plasma concentrations of glutathione S-transferase

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Summary

To assess the effect of sevoflurane anaesthesia on hepatocellular integrity, we measured plasma concentrations of glutathione S-transferase (GST) before anaesthesia and 1, 3, 6 and 24 h after the end of anaesthesia in 41 healthy, Japanese patients undergoing elective, body surface surgery. Sevoflurane (approximately 1.0 MAC) was delivered in 50–66% nitrous oxide in oxygen via a circle system, with a fresh gas flow of 6 litre min^{-1}. Ventilation was spontaneous in all patients. Mean duration of anaesthesia was 101 min. Concentrations of GST increased significantly 1 h after the end of anaesthesia ($P=0.0075$), but this was not significantly different from preoperative concentrations at 3, 6 and 24 h. Three patients developed a large secondary increase in GST concentrations at 24 h. The increase observed at 1 h was probably a result of reduced total liver blood flow; the mechanism for the secondary increase at 24 h is unclear but the possibility that products of sevoflurane biotransformation are responsible cannot be excluded. (*Br. J. Anaesth.* 1996;**77**:404–407)

Key words

Anaesthetics volatile, sevoflurane. Toxicity, hepatic. Enzymes, glutathione S-transferase.

Sevoflurane is a relatively new inhalation anaesthetic agent which has recently been licensed for clinical use in the UK[1]. It undergoes more biotransformation than isoflurane and enflurane[2], although its low blood-gas solubility coefficient and rapid elimination are thought to preclude prolonged elevated concentrations of metabolites and resultant organ dysfunction[3–5]. Studies investigating hepatic function after sevoflurane anaesthesia in humans would tend to support this view[3 4 6 7], although there are at least four case reports of sevoflurane-associated hepatotoxicity in the Japanese literature[8–11]. Standard biochemical tests of liver function however, have limited use in the detection of minor degrees of anaesthetic-related liver dysfunction. In contrast, measurement of glutathione S-transferase (GST) concentration in plasma provides a highly specific test of hepatocellular damage, and GST results correlate better with histological changes than do the aminotransferases[12]. GST concentrations increase transiently after anaesthesia with halothane[13–17] and enflurane[13] but not after isoflurane[13 14 17 18] or propofol[18 19]; the frequency of abnormal GST concentrations observed after halothane, enflurane and isoflurane anaesthesia correlates directly with the extent of metabolism and incidence of reported clinical hepatic dysfunction for these agents[13]. More recently, GST concentrations have been found to increase after sevoflurane anaesthesia in children[20], although experience with the particular GST assay used is limited.

We have measured GST concentrations in adult patients undergoing anaesthesia with sevoflurane to assess its effect on hepatocellular integrity.

Patients and methods

After obtaining approval from the Ethics Committee of Juntendo University, written informed consent was obtained from 50 healthy, Japanese patients, ASA I or II, undergoing elective general anaesthesia for body surface surgery which was expected to last 1–3 h. Exclusion criteria included obesity (body weight >20% above ideal weight), excessive alcohol intake (>3 u. day^{-1}), previous liver disease or exposure to general anaesthesia in the preceding 3 months. Patients receiving medications likely to interfere with liver function were also excluded.

Premedication was not given. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} i.v. in a dose sufficient to abolish the eyelash reflex, and suxamethonium 1 mg kg^{-1} i.v. was given to facilitate tracheal intubation if necessary. Anaesthesia was maintained with approximately 1.0 MAC of sevoflurane and 50–66% nitrous oxide in oxygen (sevoflurane MAC in 65% nitrous oxide: 1.4% for patients aged 25 yr, 1.1% for patients aged 40 yr, 0.87% for patients aged 60 yr [data on file, Abbott Laboratories]). Patients breathed spontaneously from a circle system delivered with a fresh gas flow rate of 6 litre min^{-1}; the carbon dioxide absorbent used was soda lime (Dragersorb 800, Drager, Germany). End-tidal concentrations of sevoflurane and carbon dioxide (Datex Capnomac AGM-103-30-00, Helsinki, Finland) were measured continuously throughout anaesthesia. The total dose of sevoflurane administered to each patient was calculated in MAC hours. Pentazocine was used for analgesia after surgery if required.

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LABORATORY ANALYSIS

Blood was sampled immediately before induction of anaesthesia (time 0), and 1, 3, 6 and 24 h after the end of anaesthesia for measurement of plasma GST B_1 concentration by specific radioimmunoassay, as described previously[21]. All samples from the same subject were measured in the same assay run. Inter- and intra-assay coefficients of variation were $<10\%$ and $<5\%$, respectively, over the range 2–25 μg litre^{-1}. The reference range for GST concentration is 0.5–4.8 μg litre^{-1}.

STATISTICAL ANALYSIS

Data were analysed by Friedman's two-way analysis of variance for repeated measurements. The Wilcoxon signed rank test was used to examine changes in GST concentration from time 0 to 1, 3, 6 and 24 h after induction of anaesthesia. $P<0.05$ was taken as significant. Analysis was performed with Minitab for Windows (version 10.2) run on a Dell Dimension computer.

Results

Of the 50 patients studied, nine were excluded from analysis; three patients needed to be paralysed and their lungs ventilated for surgical requirements, and six were administered extradural anaesthesia in addition to general anaesthesia. Data from the remaining 41 patients (27 male; mean age 42 (range 18–67) yr) were analysed. This sample size gave the study a power of 76% for a change in GST concentration of >0.5 μg litre^{-1}.

Thirty of these patients underwent minor or intermediate eye, nose or throat surgery; the remainder underwent relatively minor orthopaedic surgery such as arthroscopy. Forty patients received suxamethonium to facilitate tracheal intubation. The mean dose of thiopentone given for induction of anaesthesia was 263 (SD 39) mg and the mean sevoflurane dose administered for maintenance was 1.73 (range 0.59–3.18) MAC h. Mean duration of anaesthesia was 101 (45–155) min. Significant temporal changes in GST concentrations occurred after anaesthesia ($P<0.001$). Plasma GST concentrations increased significantly 1 h after the end of anaesthesia from time 0 ($P=0.0075$), but these were not significantly different from preoperative concentrations at 3, 6 and 24 h (table 1, fig. 1).

Although GST concentrations were still increased at 3 h this was not statistically significant ($P=0.069$). Ten patients had GST concentrations >4.8 μg litre^{-1} in blood samples obtained before anaesthesia; the overall pattern of GST changes after anaesthesia in these patients was similar to that in patients who had GST concentrations <4.9 μg litre^{-1} before anaesthesia. Three of these 10 patients had GST concentrations >4.8 μg litre^{-1} only in the sample obtained before anaesthesia. Three patients (7%) with preoperative GST concentrations within the reference range developed a large secondary increase in GST concentrations at 24 h (table 2). Seven of the 31 patients (23%) with preoperative GST concentrations <4.8 μg litre^{-1} developed an increased GST concentrations at some time during the study. No patient developed hypotension (mean arterial pressure $<70\%$ of pre-induction level), arterial oxygen saturation $<94\%$ or end-tidal carbon dioxide concentration >8 kPa at any time during anaesthesia.

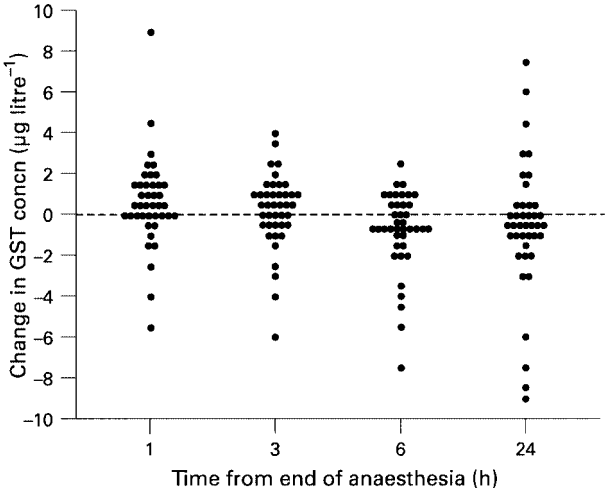

Figure 1 Individual changes in plasma gluthathione S-transferase (GST) concentrations from the preoperative sample.

Discussion

The results of this study suggest that sevoflurane influences plasma concentrations of GST after anaesthesia, confirming previous findings in children[20]. GST concentrations increased significantly from preoperative values 1 h after the end of anaesthesia, were still increased at 3 h and had decreased to preoperative concentrations at 6 and 24 h. We have demonstrated previously that GST concentrations increase 3 and 6 h after anaesthesia with halothane[13–16] and enflurane[13] but not after isoflurane[13,14]. Other workers have confirmed that GST concentrations increase after halothane but not after isoflurane anaesthesia[17] and have also demonstrated no change after propofol anaesthesia[18,19]. Reduced liver blood flow is believed to be responsible for these increases; alternative explanations such as variation in GST concentration throughout the day or reduced clearance of GST have been discounted previously[22]. Several studies have shown that sevoflurane has little overall effect on hepatic blood flow in experimental animals[23–26], although if hepatic arterial

Table 1 Median (1st, 3rd quartiles) glutathione S-transferase concentrations (μg litre^{-1}) in 41 patients receiving sevoflurane anasthesia. *$P < 0.01$ compared with concentrations before anaesthesia

Before anaesthesia	1 h	3 h	6 h	24 h
2.8 (2.0, 5.0)	3.9* (2.6, 5.3)	3.5 (2.6, 5.2)	2.8 (2.1, 3.8)	3.3 (1.6, 4.6)

Table 2 Plasma concentrations of glutathione S-transferase (μg litre^{-1}) in patients who developed a large secondary increase at 24 h

Before anaesthesia	1 h	3 h	6 h	24 h
1.4	2.6	2.6	2.8	7.3
2.8	4.9	4.4	4.0	10.2
4.7	6.3	7.2	5.8	9.4

flow is compromised there may be a smaller margin of safety against hypoxia with sevoflurane compared with halothane and isoflurane[27]. There is evidence in humans to suggest that sevoflurane reduces total hepatic blood flow[28], although this has not been confirmed by other workers[29 30]. Our findings appear to support the view that sevoflurane reduces hepatic blood flow in humans.

Three patients (7%) developed a much larger secondary increase in GST concentrations at 24 h. In a previous study, 18% of patients anaesthetized with halothane and 10% of those who received enflurane developed similar increases at 24 h; this later increase did not occur in patients after isoflurane anaesthesia[13]. The mechanism for these increases at 24 h is unclear but the possibility that products of biotransformation (including those of sevoflurane) are responsible cannot be excluded. The overall extent of sevoflurane metabolism in humans is approximately 5%[2 3], resulting in the formation of hexafluoroisopropanol (HFIP) and fluoride ion. Neither of these products is likely to be responsible for initiating hepatic damage[5]. Sevoflurane reacts with carbon dioxide absorbents resulting in generation of breakdown products. Five degradation products have been identified *in vitro*[31], although only compound A (and to a lesser extent compound B) is produced under conditions likely to be encountered clinically. Factors which alter the concentration of compound A include fresh gas flow, temperature of the soda lime and concentration of sevoflurane in the circle system. Low fresh gas flows are associated with an increase in temperature of the soda lime and increased concentrations of compound A which increase further with prolonged anaesthesia[32 33]. In this study, a fresh gas flow of 6 litre min^{-1} was used to prevent the build up of a significant concentration of compound A. While there is debate about the potential for compound A to induce renal damage, there is no suggestion that it may initiate hepatic damage[34]. We do not believe that compound A is responsible for the observed increase in GST concentration.

The reference range for GST concentration in adult patients in the UK is 0.5–4.8 μg $litre^{-1}$; the range for the Japanese population is not known. As 10 patients (20%) in this study had preoperative GST concentrations >4.8 μg $litre^{-1}$, it could be argued that there is a different reference range for Japanese patients. However, the pattern of GST response after anaesthesia was similar if these patients were excluded from analysis, and therefore the overall conclusion from this study is unaltered. Three of these 10 patients had GST concentrations > 4.8 μg $litre^{-1}$ in the preoperative sample only, suggesting that in these patients increased GST concentrations may have resulted from fasting, as has been described previously[22].

We conclude that sevoflurane anaesthesia is associated with a transient increase in plasma GST concentrations after anaesthesia, reflecting a minor degree of impaired hepatocellular integrity. Some patients develop increased GST concentrations 24 h after sevoflurane anaesthesia; the reasons for this secondary increase are unclear and require further investigation.

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